Gynecologic Cancer InterGroup
Cervix Cancer Research Network

HPV & HIV considerations in Africa

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Cervix Cancer Education Symposium, January 2019, South Africa

Cervical Cancer Prevention on WHO Agenda

19th May 2018: Cervical cancer is one of the most preventable and treatable forms of cancer as long as it is prevented with HPV vaccination, detected early, and managed effectively. Prevention and early treatment are highly cost-effective. Worldwide however, cervical cancer remains one of the gravest threats to women's lives, and globally, one woman dies of cervical cancer every two minutes. This suffering is unacceptable, and cannot continue. In recognition of this, WHO Director-General, Dr Tedros Adhanom Ghebreyesus today made a global call for action towards the elimination of cervical cancer.

Read the call to action
pdf, 82kb

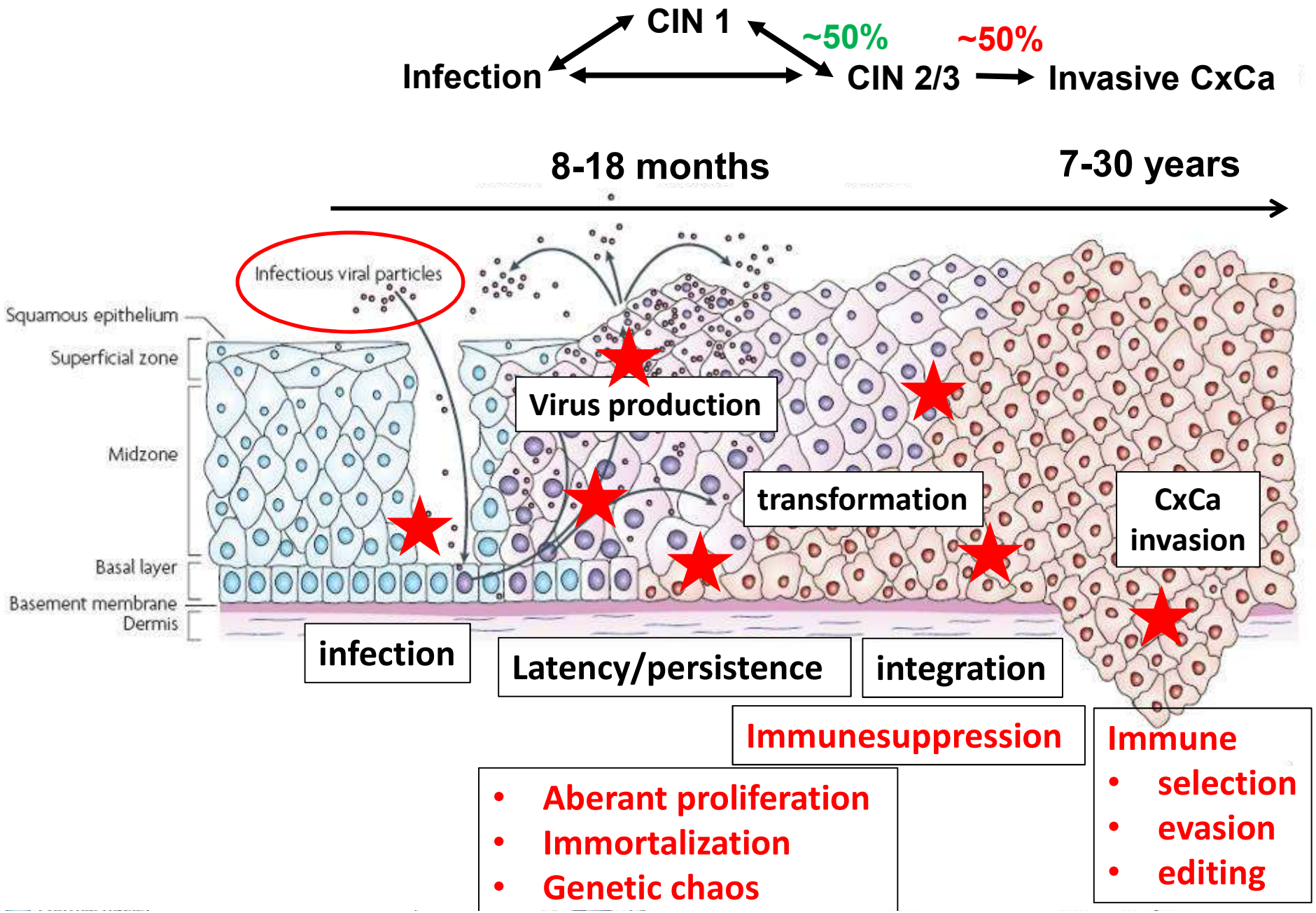
Dr Tedros Adhanom Ghebreyesus, WHO Director-General

Read the call to action
pdf, 82kb

Agenda

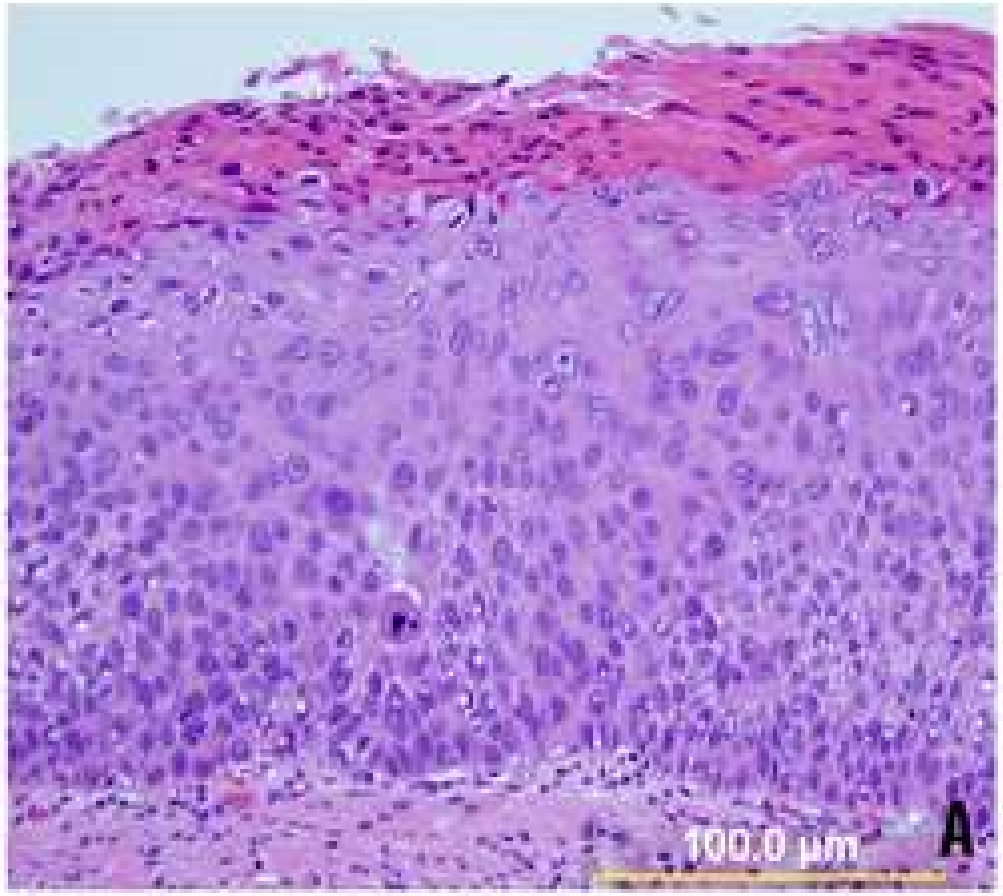
- HPV biology & epidemiology
- HPV in ART era
- Vaccination and Screening

Progression from Infection to Cervical Cancer



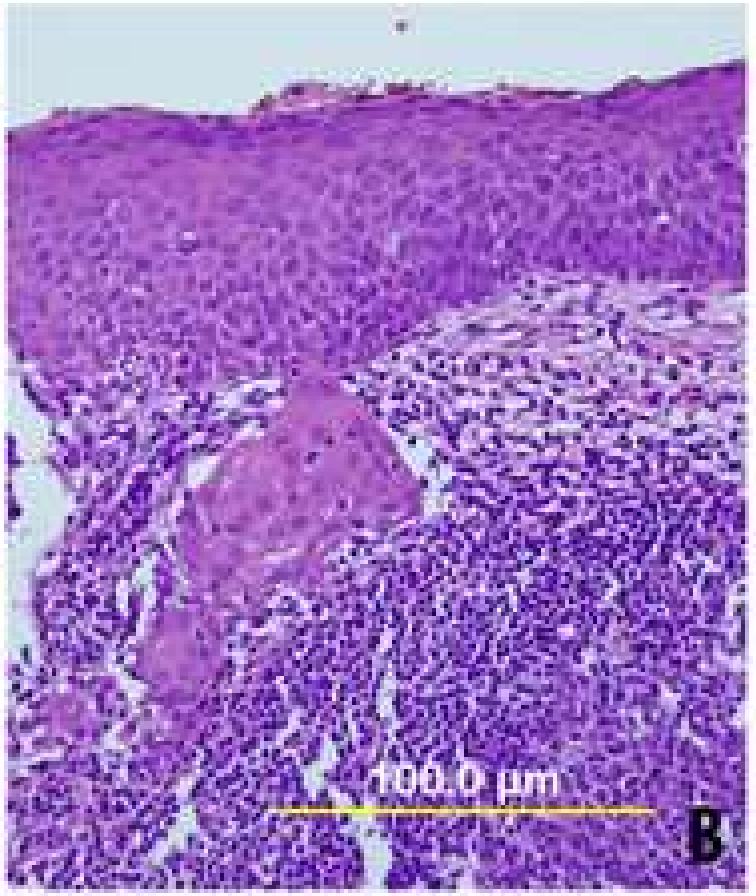
Natural Immunity: Lymphocytic Infiltrates

CIN



minor

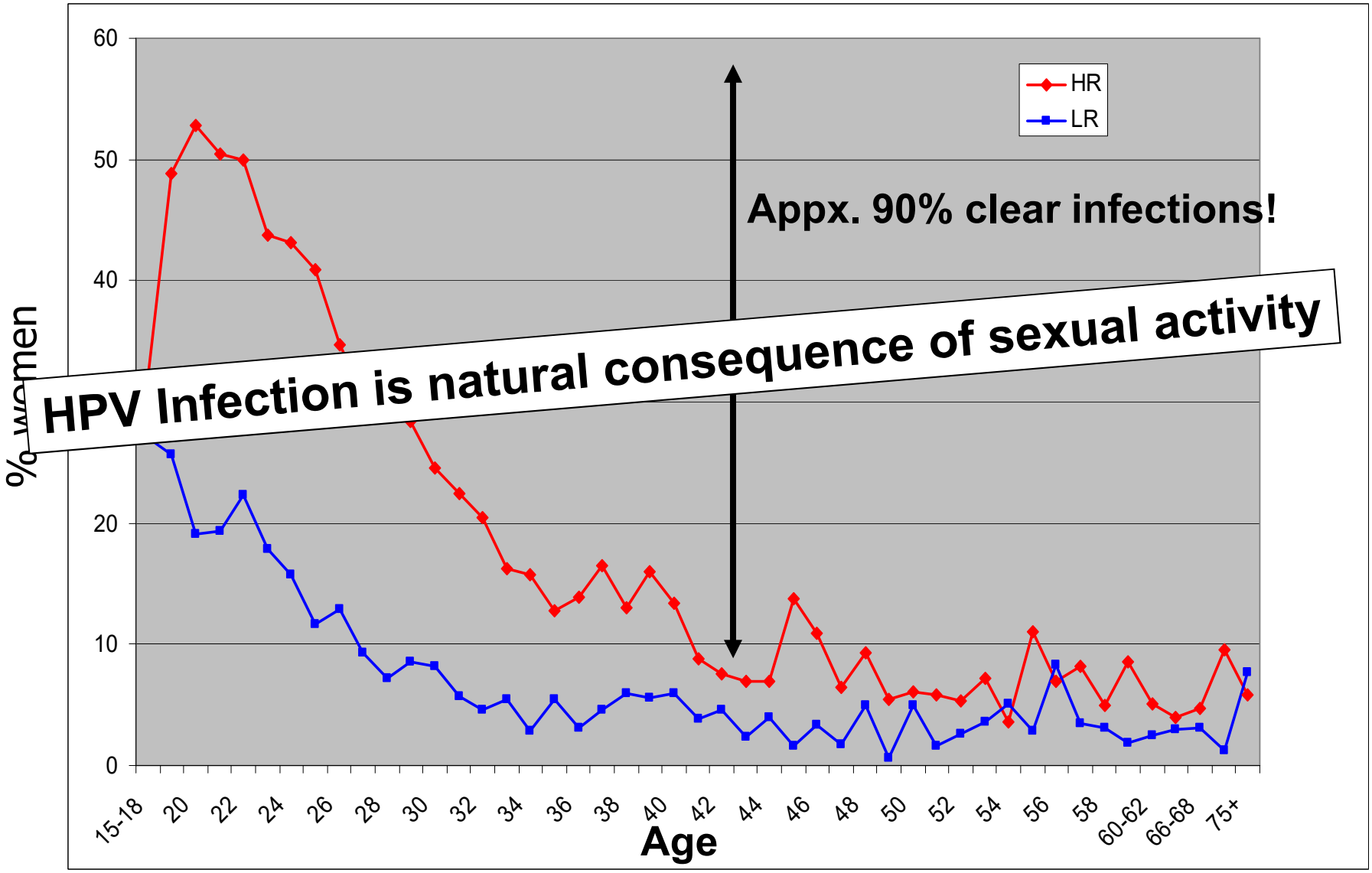
CxCa



major,
but exclusively peritumoral

HPV-Prevalence and Age

11.851 Women in Demark



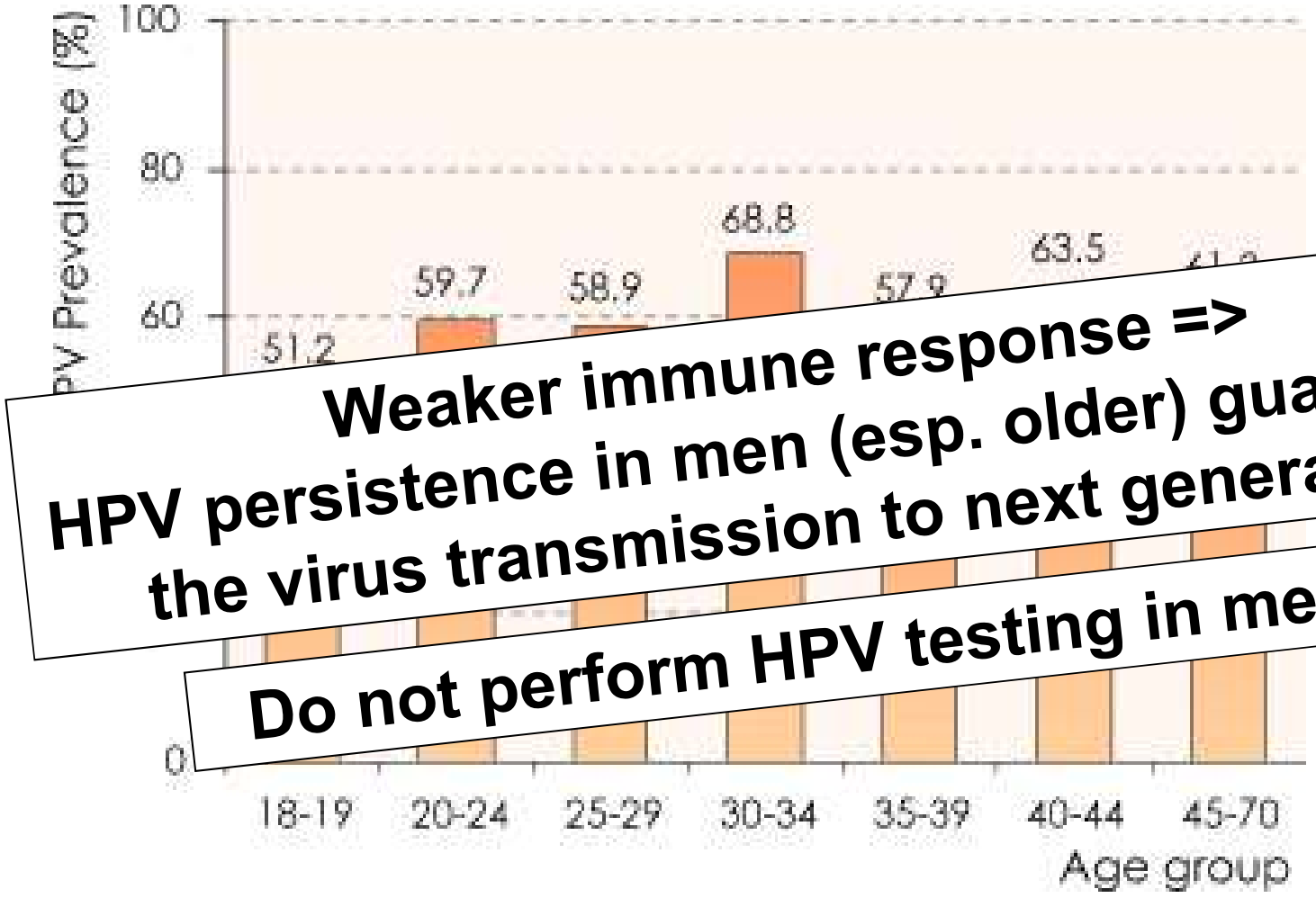
Krüger-Kjaer, et al. 2007

Baseman and Koutsky. J Virol:32S. 2005

HPV detection (any type) per age group in men from Brasil, Mexico and USA

Giuliano et al., Vaccine 26 suppl.10 (2008) K17-K28

HPV detection (any type) per age group in men from Brasil, Mexico and USA



Weaker immune response => HPV persistence in men (esp. older) guaranties the virus transmission to next generation

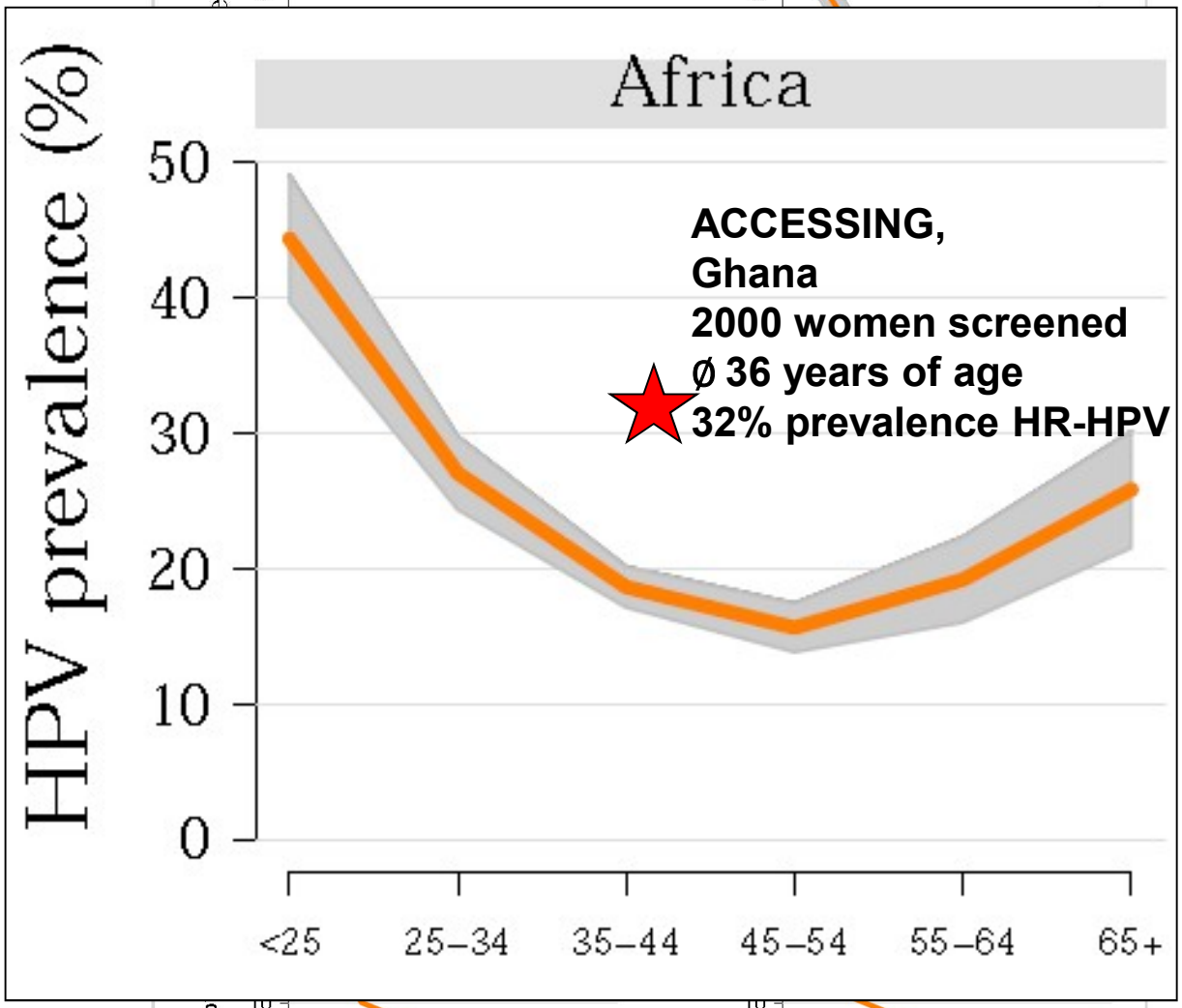
Do not perform HPV testing in men

Giuliano et al., Vaccine 26 suppl.10 (2008) K17-K28

HPV prevalence in women by world region

20%-50% in 25 years old

5%-30% in >40 years old



ICO HPV Information Center

Risk of Human Papillomavirus–Associated Cancers Among Persons With AIDS

- 499 230 individuals diagnosed with AIDS 1980 to 2004 were linked with with cancer registries in 15 US regions

- **8 – 10-fold increased risk for cervical carcinoma**
- **60 – 70-fold increase risk for anal cancer**
- **1.6-fold increase risk for oropharyngeal cancer**

- **104% increase for invasive HPV-associated cancers in ART Era** (after 1996) compared to pre ART, whereas incidence of other cancers was stable over time.

Chaturvedi et al., 2009

Increase of HR-HPV cancer in the era of ART: The U.S. Military Natural History Study (1985– 2008).

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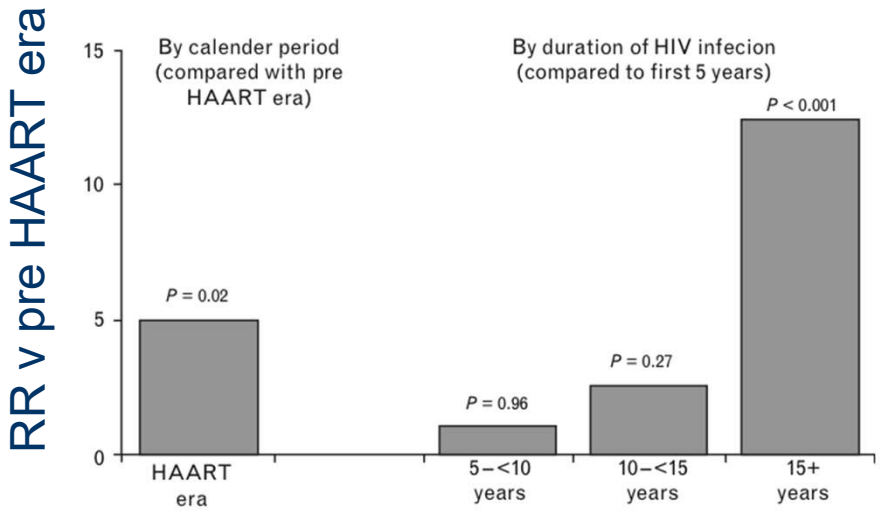
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

- **Follow up of 4506 HIV+ men, total of 38000 person-years**

Anal cancer rates jump

from	**11/100.000 person years**	**(1985 – 1996, no ART)**
to	**55/100.000 person years**	**(1997 – 2008, ART era)**



⊘ **42 years at diagnosis**

Significant risk factors:

Long Duration of HIV infection >15 years

low CD4 nadir <200

History of opportunistic disease

Crum-Cianflone et al. 2010 AIDS

HIV causes more rapid progression to Cervical Cancer

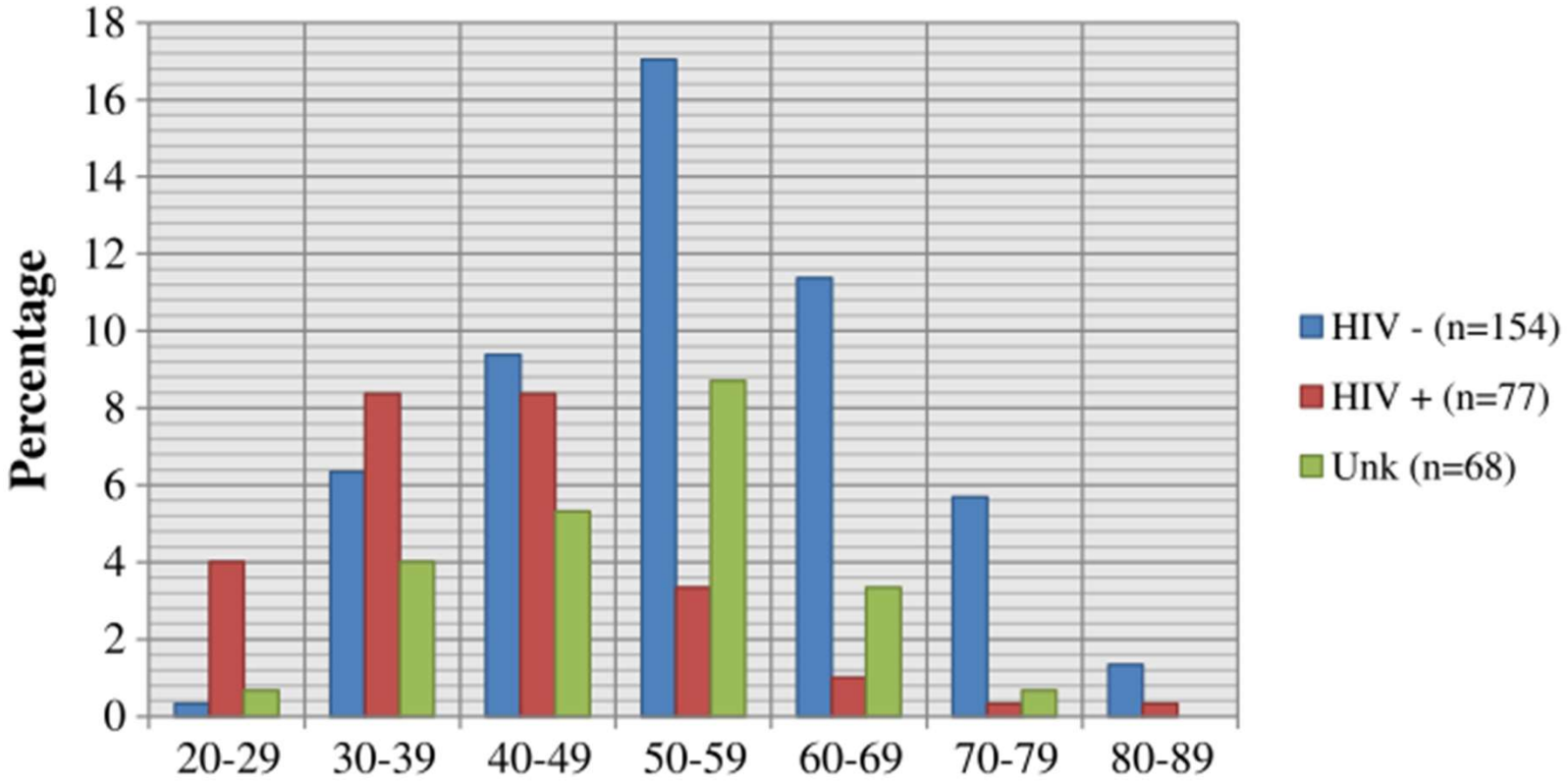
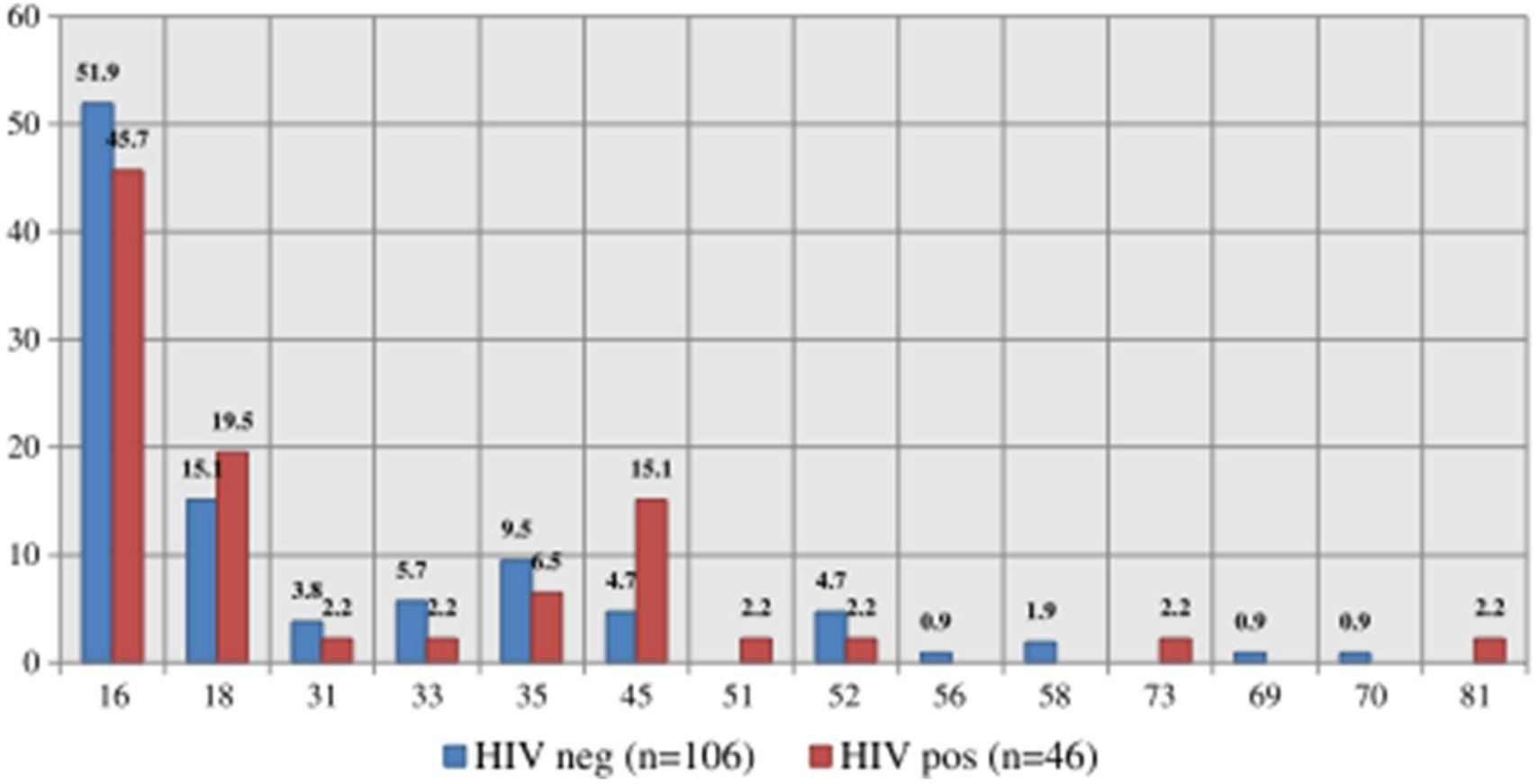


FIGURE 1. Age distribution and HIV prevalence for the study population.

Van Ardt et al., 2015

HR HPV prevalence in South African Cervical Cancer cases



Van Ardt et al., 2015

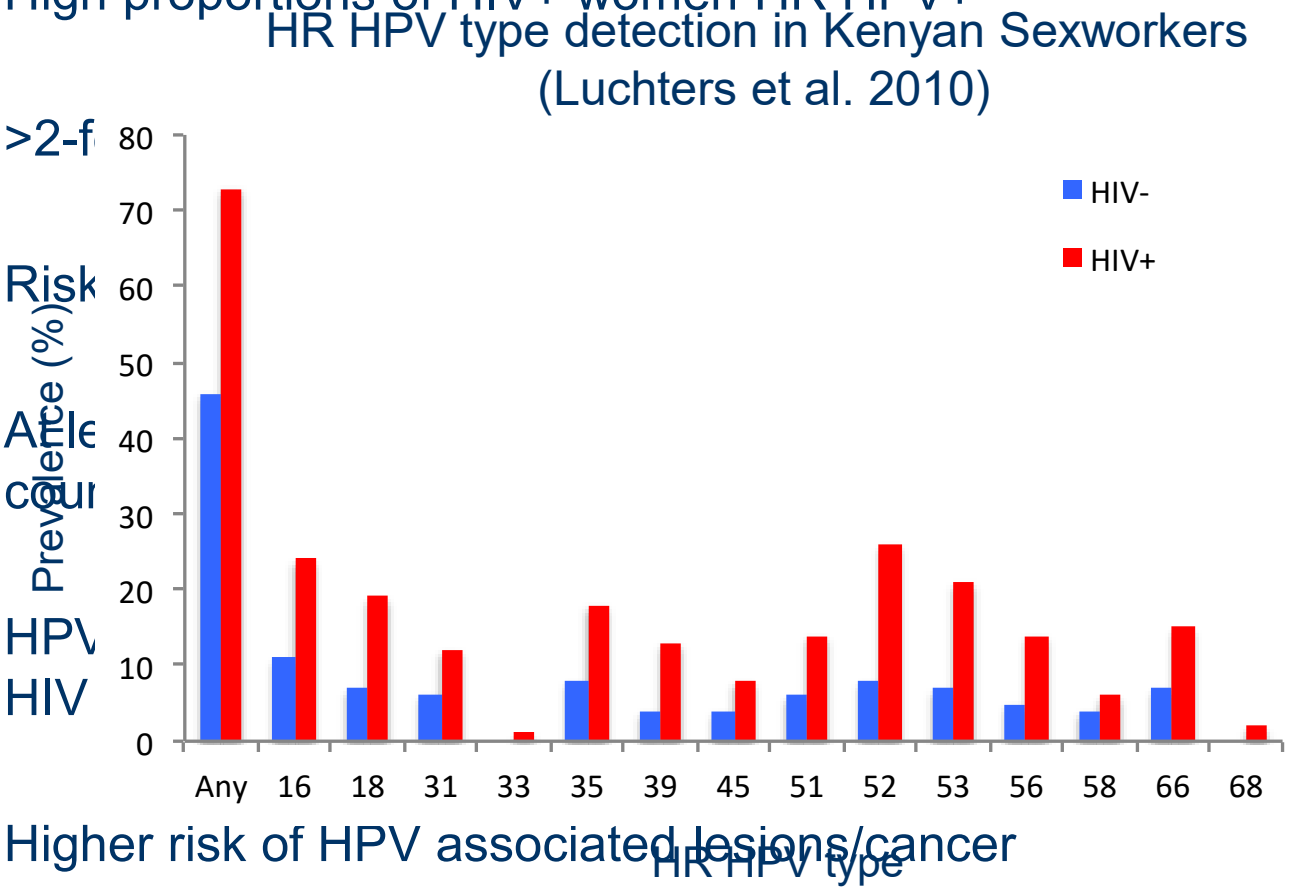
High HPV prevalence in HIV-positive

	HIV+ (n=100)	HR Gruppe (n=150)
CIN2+	14% (14)	3% (5)
HPV+	80% (80)	38% (57)
hrHPV	72% (72)	30% (45)
Multi hrHPV	47% (47)	17% (25)
Top 10 HPV Typen	16 (34%) 52 (17%) 31 (14%) 35, 39, 82 (10%) 18 (9%) 53, 70 (8%) 45,73 (7%)	52 (12%) 16 (11%) 59 (10%) 51 (7%) 39 (6%) 66 (5%) 45, 53 (4%) 35, 53, 58, 70 (3%)

ACCESSING Study, Ghana

HIV infection is linked to high HR HPV type diversity detected in cervical samples

- High proportions of HIV+ women HR HPV+
- >2-f Workers
- Risk d increased
- Atte · (CD4 T cell cou
- HPV compared to HIV
- Higher risk of HPV associated lesions/cancer



Luchters et al., 2010 BMC Inf. Dis; Sahasrabuddhe 2007 & many others

HIV-HPV co-infection

- Lower CD4 count at ART initiation was associated with greater risk of KS, lymphoma, and human papillomavirus–related cancer

- recommendations for earlier HIV diagnosis followed by prompt ART initiation along with ongoing aggressive cancer screening and prevention effort

Crum-Cianflone et al., 2010 AIDS

HAART initiation only slightly decreases incidence of cervical abnormalities (but prolongs life!)

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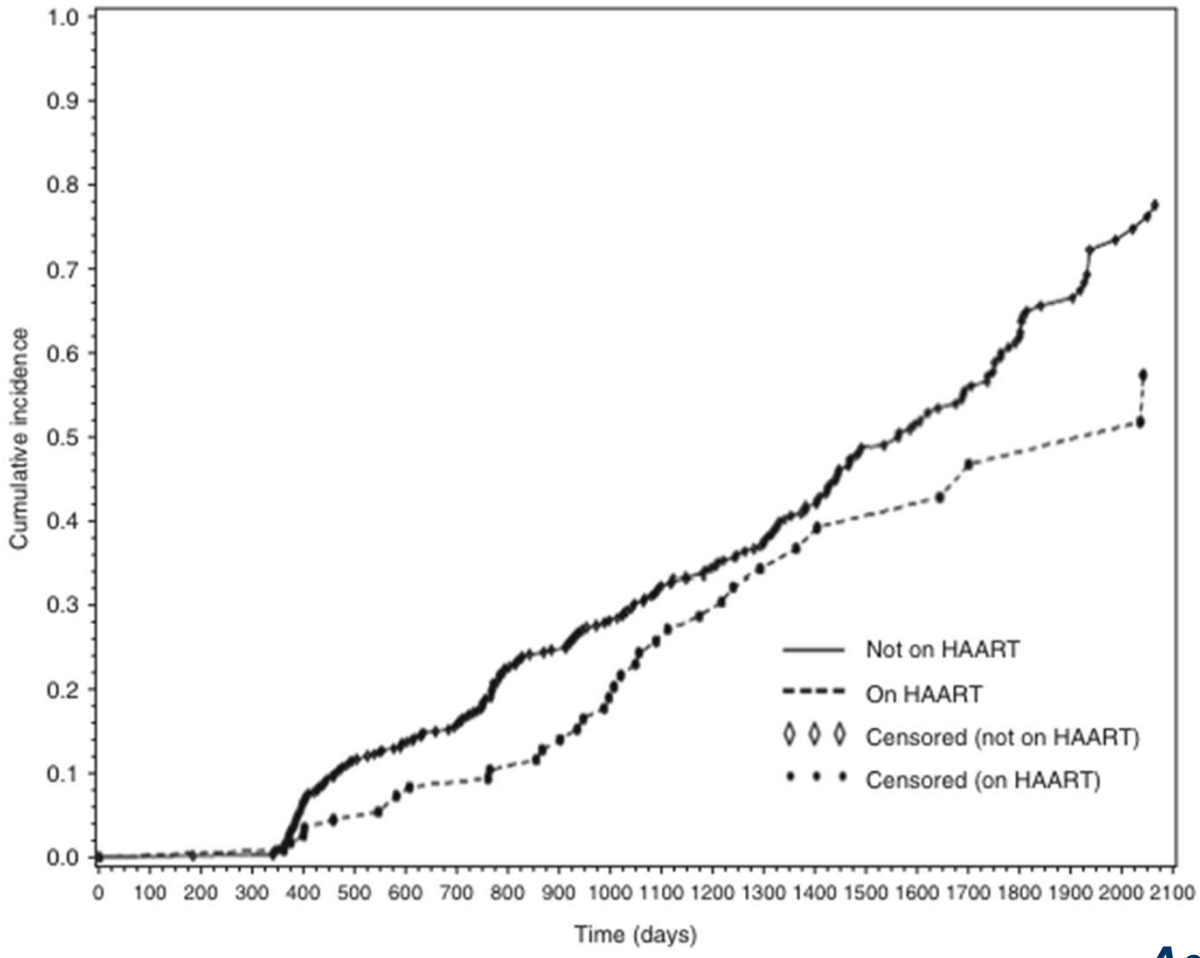

compare drop in tuberculosis incidence after HAART

Adler et al., 2013

Increased acquisition and decreased clearance of oncogenic HPV

- HIV infection is associated with increased acquisition (Hazard Ratio, 2.3; P = 0.03), and decreased clearance (Hazard Ratio, 0.4; P < 0.001) of HPV DNA

- HAART increases the likelihood of regression (from present to absent) of cervical SIL (HR, 3.3; P = 0.02) and increased the clearance of oncogenic HPV types other than HPV-16 or HPV-18 (HR, 2.2; P = 0.01)

Blitz et al., 2013 JID

Take Home message, part 1

- Risk for HPV-associated premalignant dysplasia is dramatically increased in HIV+ subjects
- HIV is associated with >10 years younger median age at presentation of Cervical cancer – vigorous CC screening is indicated
- Nadir CD4 count before HAART correlates with risk for CC progression.
- HAART initiation substantially increases survival of HIV patients, but only slightly reduces “per annum incidence risk” of premalignant lesions and cervical cancer and only slightly improves rate of lesion regression (mainly LSIL)

Take Home message, part 1

- HIV is associated with high diversity of HPV types in female reproductive tract

- Most studies show a high prevalence of HPV16 in Cervical cancer also in HIV+ women. However, a variety of other types (18, 45, 35) also make up for a significant portion of CC.

- In contrast, high grade lesions more often associated with none-HPV16/18 HR HPVs – HSIL and CC should be differentiated !

Potential for CxCa prevention

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HPV vaccination
Immunocompromised HIV+ => effect?

Screening for pre-cancer, and downstaging
- **VIA**
- **HPV-based**
- **Biomarker-based**

Vaccines: L1 Virosomes VLP+Adjuvans

- Cervarix: bivalent HPV16 and 18; 93% pre-cancer, 70% CxCa
- ~~Gardasil: quadrivalent~~ HPV6, 11, 16, 18; 46% pre-cancer, 70% CxCa,
- Gardasil 9: nonavalent HPV 6, 11, 16, 18, +31, 33, 45, 52, 58 89% pre-cancer, 90% CxCa,

Recommendation:
2 dose schedule 9-14 yrs
(0 and > 6 months)

3 dose schedule 15-18 yrs
(0, 2, >6 months)
Girls and women
Boys and men!!!

Older women and men?

RKI Epidemiol Bull.,
2007, 2014, 2018

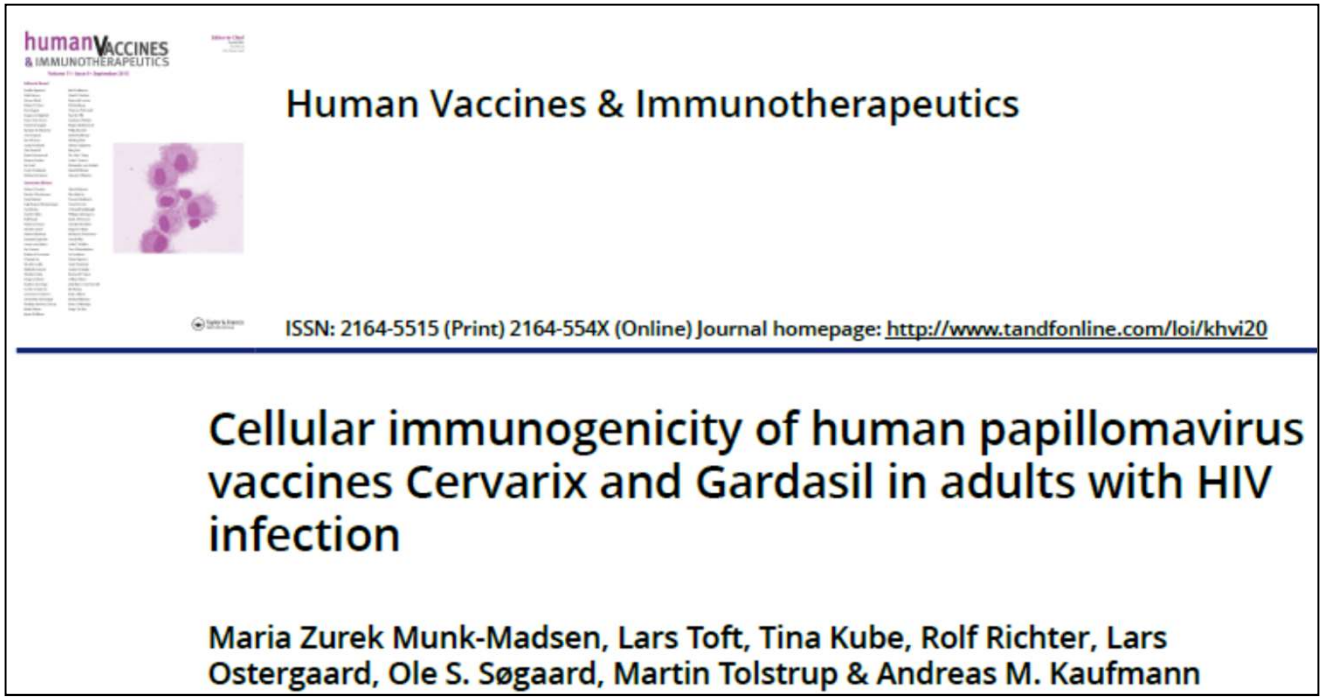
International Papillomavirus Society (IPVS)
Policy Statements

IPVS Policy statement on safety of HPV vaccines
Papillomavirus Research 2 (2016) 9–10

The Cape Town Declaration on the Prevention of Human Papillomavirus Disease
https://ipvsoc.org/policy-statements/ (acc.1.11.2018)

HPV vaccination of immunocompromised hosts
Papillomavirus Research 4 (2017) 35–38

IPVS statement moving towards elimination of cervical cancer as a public health problem
Papillomavirus Research 5 (2018) 87–88



Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

Cellular immunogenicity of human papillomavirus vaccines Cervarix and Gardasil in adults with HIV infection

Maria Zurek Munk-Madsen, Lars Toft, Tina Kube, Rolf Richter, Lars Ostergaard, Ole S. Søgaard, Martin Tolstrup & Andreas M. Kaufmann

Hum Vaccin Immunother. 2018;14:909

Comparison of the Immunogenicity and Reactogenicity of Cervarix and Gardasil Human Papillomavirus Vaccines in HIV-Infected Adults: A Randomized, Double-Blind Clinical Trial

Lars Toft,[1] Merete Storgaard,[1] Martin Müller,[2] Peter Sehr,[3] Jesper Bonde,[4,5] Martin Tolstrup,[1] Lars Østergaard,[1] and Ole S. Søgaard[1]

J Infect Dis. 2014; 209:1165

VACCINATION COVERAGES BY REGION

Through 2014, 64 countries nationally, 4 countries in some regions, and 12 overseas territories had implemented publicly funded national HPV vaccination programs

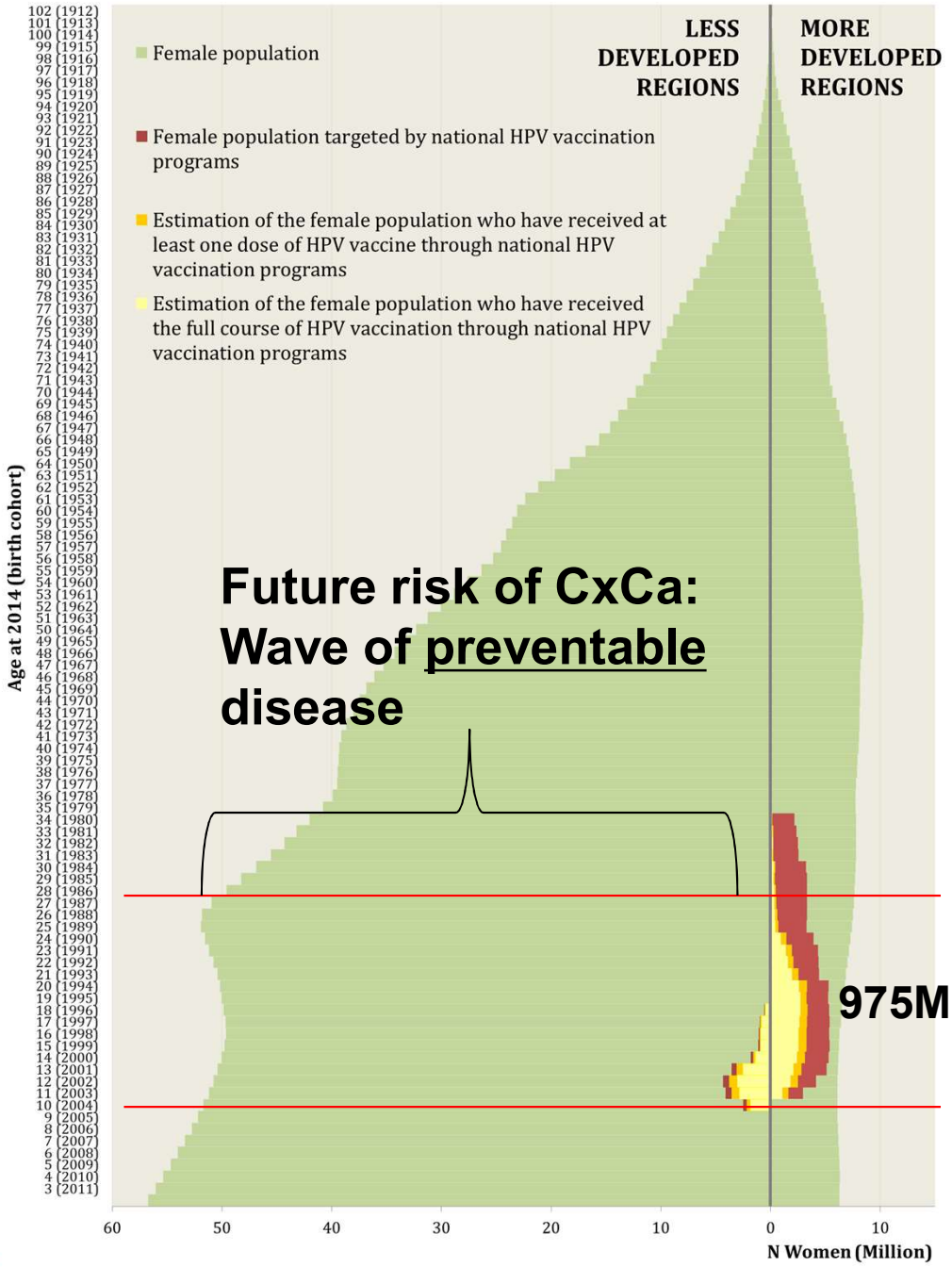
WOMEN VACCINATED AGAINST HPV THROUGH PUBLICALY FUNDED VACCINATION PROGRAMS

1-DOSE+ VACCINATION

By 2014, **59M** women received at least **one-dose HPV vaccine** through national HPV vaccination programs.

One-dose+ coverage:

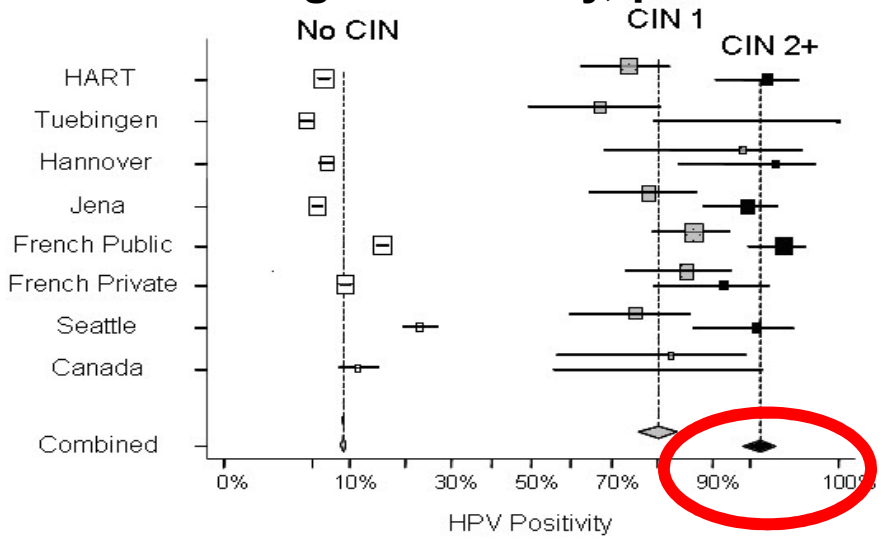
- **50%** of targeted cohorts in developed countries
- **<5%** in less developed countries



Bruni et al. 2015

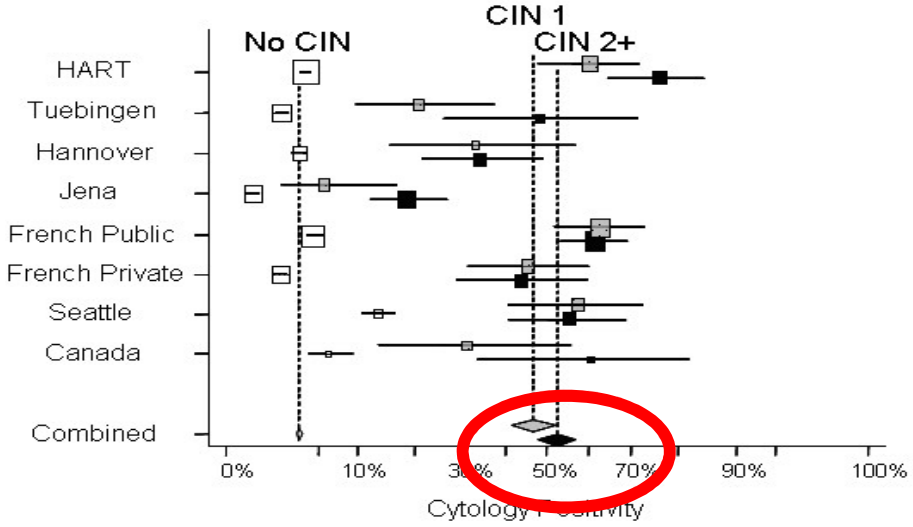
SCREENING: Sensitivity and Specificity of HPV test vs cytology

HPV Test: high sensitivity, problem low specificity



PCR–based
Technically problematic
Many HPV positives

Cytology: Problem sensitivity, high specificity



Microscopically read
logistics
training
subjective

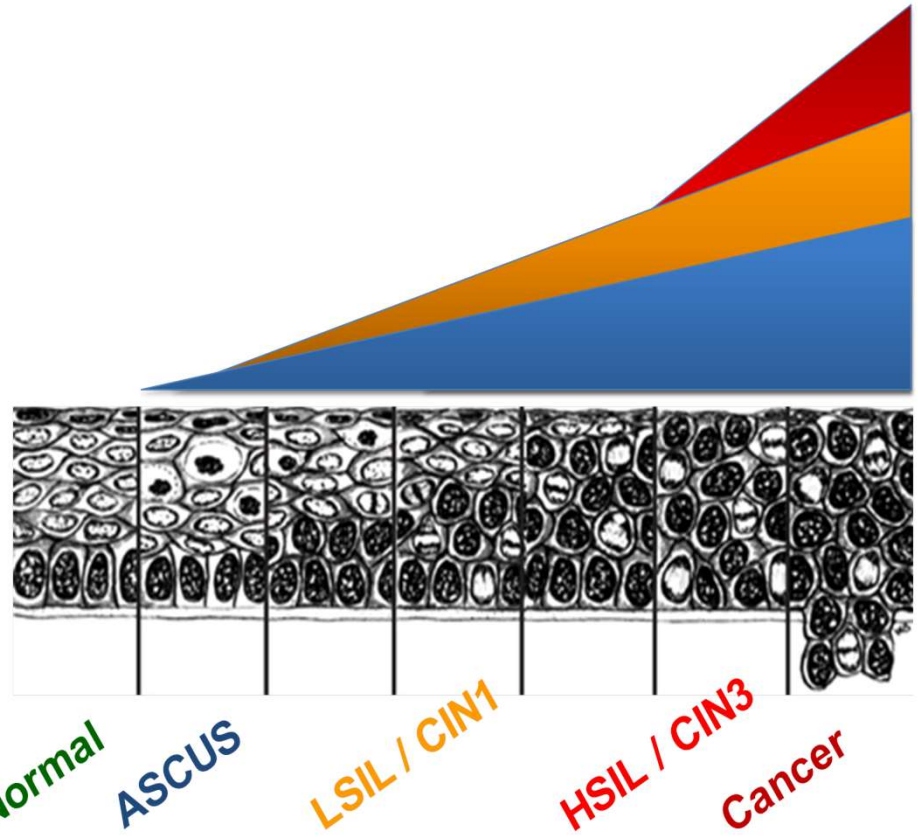
Cuzick et al., Int J Cancer 2008

Use of Biomarkers!

- HPV Oncogene expression (E6/E7) => protein assay
- Methylation markers of cellular and HPV genes => msPCR
- miRNA expression => PCR
- Cellular biomarker expression => QuantiGene

- NOT detection of a HPV infection…
- BUT biological processes leading to cellular transformation and cancer
- Circumventing prevalence problem in HIV+,
- focussing resources on women with dysplasia!

E6 Oncoprotein a Biomarker of Oncogenic Activity



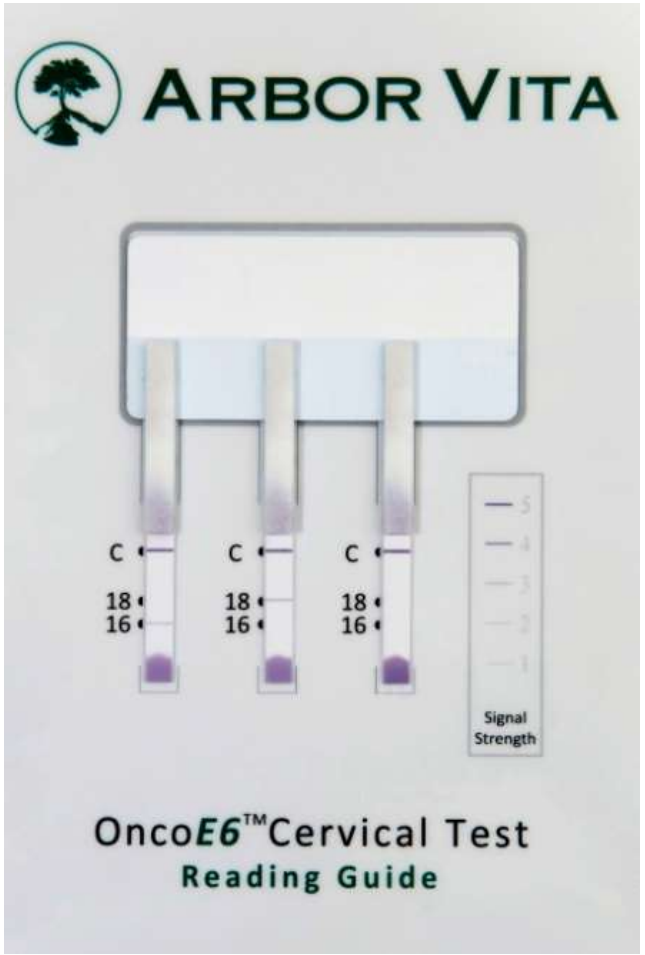
Arbor Vita E6 Cervical Test

- Lateral flow Immunoassay Test
- Detection of HPV16 and 18 w/typing
- Semiquantiative reading
- LMIC adapted

• Sensitivity	for CIN3+	53.5%
	for CxCa	91.7%
• Specificity	for CIN3+	98.9%
• PPV	for CIN3+	40.8%
• NPV	for CIN3+	99.37%

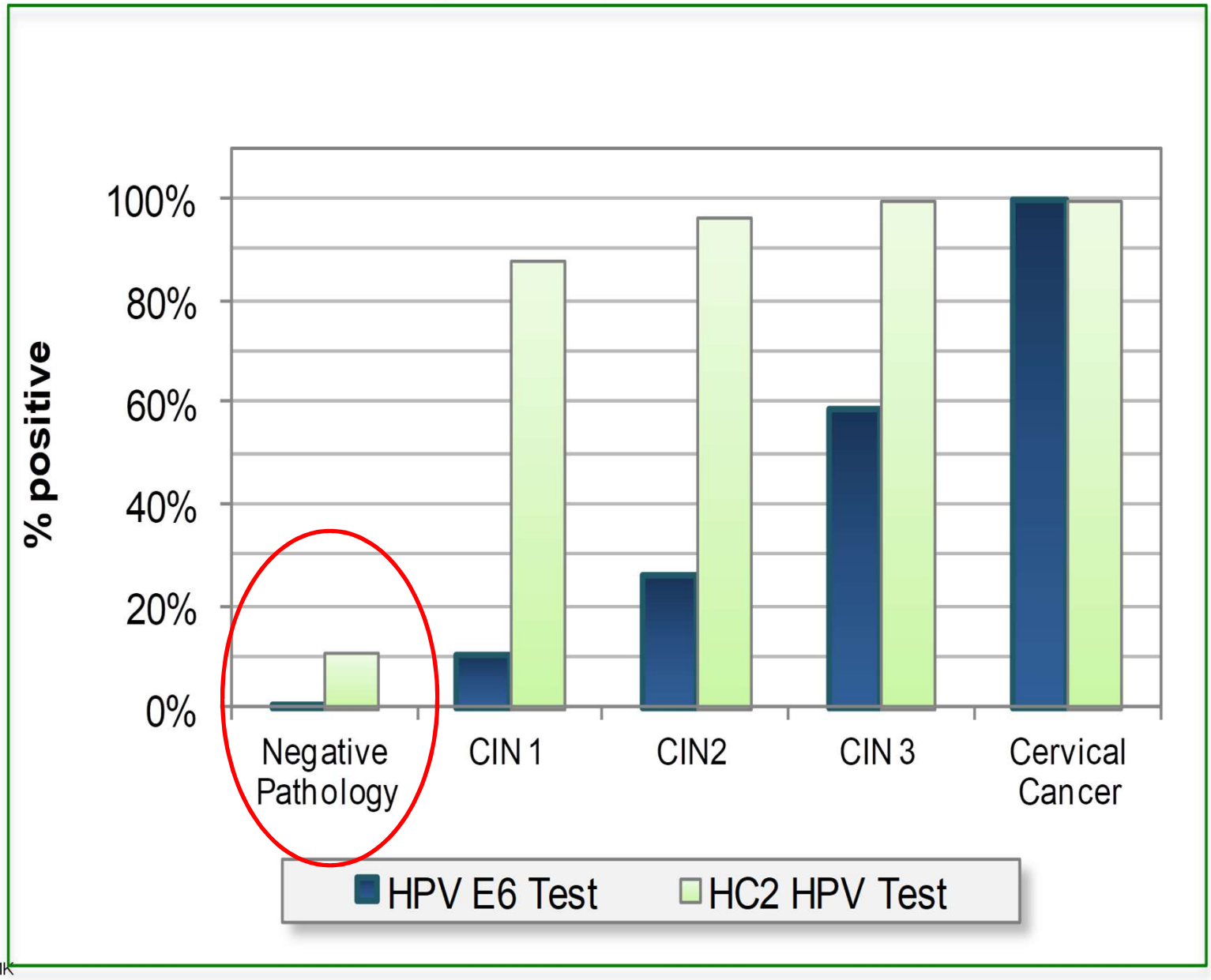
⇒ **Screening test**

⇒ **Triage test for 16/18 positives**



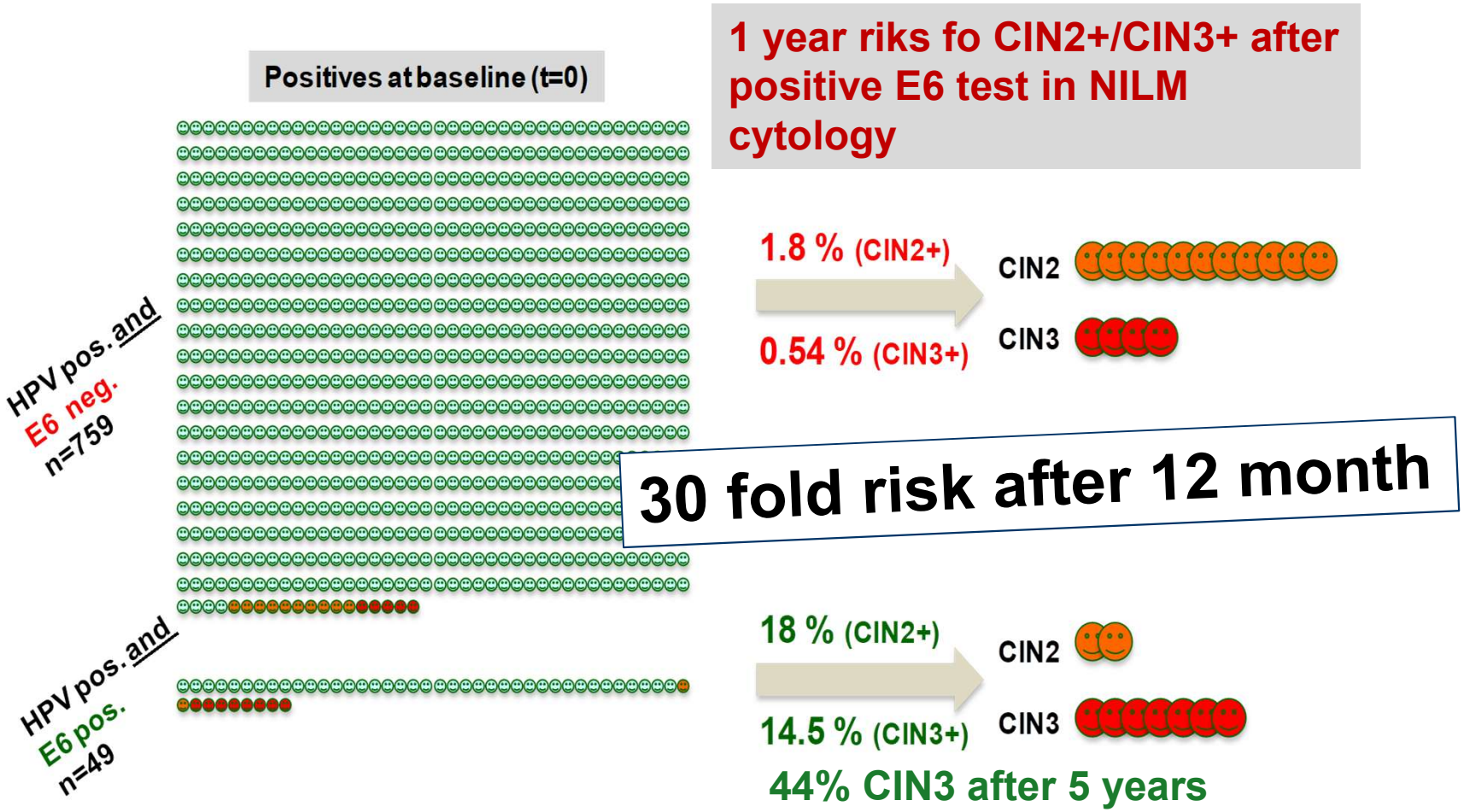
Zhao et al., 2013

Positivity compared to HC2



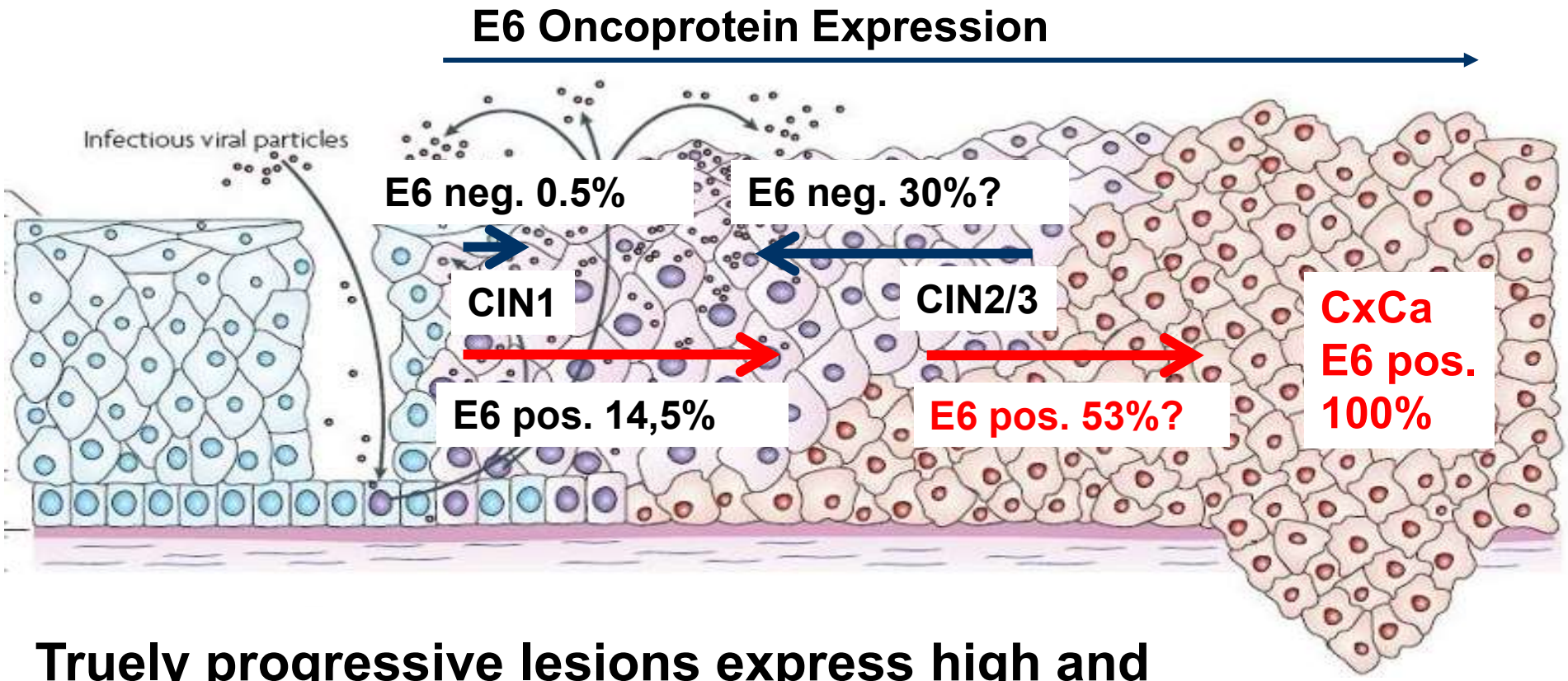
OncoE6™ positive test and risk for future disease

Risk in follow-up study, 1st year



Zhao et al., 2013

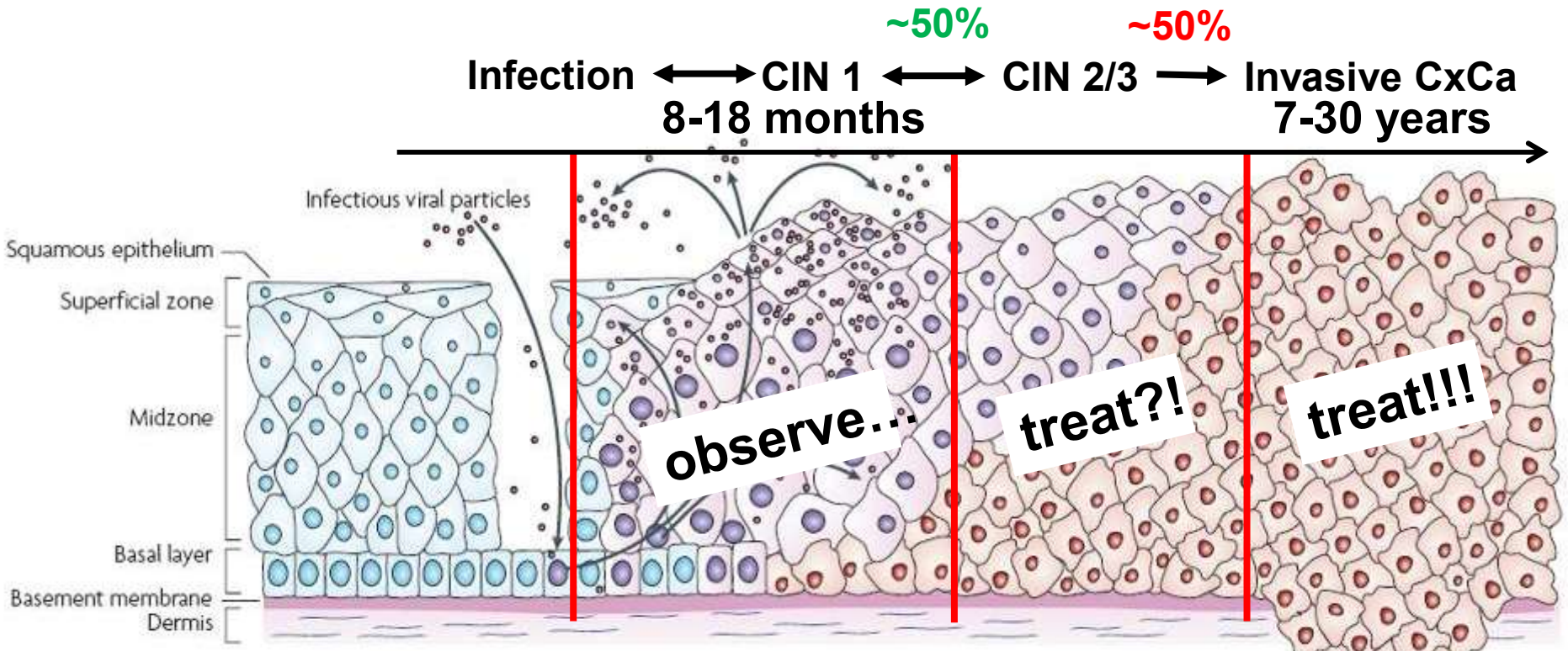
Biomarker for high-grade and progressive dysplasia



Truely progressive lesions express high and sufficient amount of oncoprotein to be detected.

The biological-clinical problem: Identifcation of

HPV Association?, Dysplasia Stage?, Progression?



mRNA of: HPV Type present? Quantify! + Specific Biomarker set 1 + Specific biomarker set 2 + Specific biomarker set 3

PAP Cytology (~50% Sensitivity)

HPV DNA Test (>95% Sensitivity but low Specificity: ~8,5% CIN3)

Considerations

- High HPV prevalence in HIV+ compromises HPV-based screening

For LMIC

- Test should by specific for high grade lesion, true progressors
- New test systems (oncoprotein, biomarkers) show such potential
- Technical feasibility and low cost
- Self-sampling compatible, high throughput, quick result (POC test?)
- Prognostic value


Thank you!
World Health Summit 2018, Berlin, Germany